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Editorial

EDITORIAL

Individualising goal-directed haemodynamic therapy: future iterations will require novel trial designs

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Summary

Variants of perioperative cardiac output-guided haemodynamic therapy algorithms have been tested over the last few decades, without clear evidence of effectiveness. Newer approaches have focussed on individualisation of physiological targets and have been tested in early efficacy trials. Uncertainty about the benefits remains. Adoption of novel trial designs could overcome the limitations of smaller trials of this complex intervention and accelerate the exploration of future developments.

Keywords: arterial waveform analysis; cardiac output; fluid responsiveness; goal-directed haemodynamic therapy; perioperative outcomes; stroke volume

In the nearly 40 years since the first studies of goal-directed haemodynamic therapy (GDHT) by Shultz and Shoemaker, what have we learnt? Managing patients' haemodynamic status remains a core activity of perioperative clinicians and is thought to have an impact on patient outcomes. The search for better ways of achieving adequate tissue perfusion without iatrogenic harm has gone on for many decades. But does it make any difference?

GDHT, a shorthand term for the use of advanced monitoring and treatment algorithms guided by physiological targets, has been a key intervention in this long investigative journey, yet without definitive conclusions about its effectiveness. GDHT remains a complex intervention with multiple component parts, including the monitoring technology, physiological target, treatments used to achieve the defined goals, timing of the interventions, and the populations to which it is applied. Mixed results from more recent trials[1–4] have driven researchers to investigate further iterations of these component parts.

In this issue of the *British Journal of Anaesthesia*, Funcke and colleagues,[5] who are experienced researchers in this area, report the findings of the iPEGASUS randomised controlled trial (RCT) of perioperative GDHT. Across five hospitals, 364 higher risk patients undergoing major open abdominal surgery were randomised to usual care or a GDHT intervention during and for 8 h after surgery.

Like many recent trials of GDHT, a minimally invasive approach to cardiac output monitoring using arterial waveform analysis was used. The algorithm was based on a cardiac index target, with fluid boluses and dobutamine the protocolised treatments. The novelty of this trial is the use of 'optimised post-induction cardiac index' as the target of the algorithm. Most contemporary GDHT trials aim to improve volume-dependent cardiac function throughout the intervention period by initially giving fluid boluses until there is no

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further increase in stroke volume, or alternatively using dynamic preload markers, such as stroke volume variation, throughout the respiratory cycle to indicate the likelihood of fluid responsiveness. Inotropes or vasopressors can then be added if the primary or secondary (e.g. arterial blood pressure) targets have not been met. Earlier studies defined fixed global oxygen delivery targets for all patients.[6]

Alternative approaches have been investigated previously by this group and others, measuring cardiac output (or oxygen delivery) before the onset of general anaesthesia and using this baseline value as a target during the subsequent intervention period.[7,8] This approach is argued to individualise physiological targets more closely and therefore reduce the potential for harm caused by attempting to achieve supranormal values of cardiac output or oxygen delivery. This group's previous investigation using this approach showed benefit, albeit in a small (n=188) efficacy trial.[7]

In this study,[5] each participant's post-induction cardiac index was used as the physiological target, once any requirement for plasma volume expansion was satisfied according to pulse pressure variation (PPV) measurements. The authors' rationale for using this target is that energy expenditure, and therefore the cardiac output required under general anaesthesia, is less than when awake. However, a lowest acceptable limit of cardiac index was set (2.5 L min^{-1} m^{-2}), with dobutamine added if this was not achieved. Once the optimised post-induction cardiac index was established, investigators aimed to maintain cardiac index at this value or higher during surgery and for 8 h after. In the event that cardiac index decreased below this limit, investigators administered fluid boluses if PPV was >12%, or dobutamine if not. Broad recommendations included guidance to maintain mean arterial pressure above 65 mm Hg, using vasopressors if required.

Around 50% of intervention participants required fluids to optimise the initial post-induction cardiac index. Administered fluid volumes are similar to other GDHT trials, both in the absolute volumes used and the modest increase in volume in the intervention group. Just over 40% of participants in the intervention group received dobutamine to maintain cardiac index (and none in the control group), and the vast majority of participants in both control and intervention groups received vasopressors.

Contrary to the authors' hypothesis, more intervention group participants experienced the primary composite outcome of moderate to severe complication within 28 days of surgery, and this finding was consistent at earlier timepoints within the postoperative recovery. The finding was also observed in a per protocol analysis. The authors conclude that maintenance of optimised post-induction cardiac index should not be pursued as a GDHT approach looking to reduce postoperative morbidity.

Several important strengths of this trial should be noted. Given the complexity of GDHT as an intervention, if an approach does not bring apparent benefit, the first question is whether it was performed as intended. Here the authors have carefully monitored treatment compliance and found it to be very good. This is consistent with the absence of benefit in the per protocol analysis. A reasonable compromise has been made in defining control group care, encompassing guidance for all participants on managing blood pressure, heart rate, and ventilation to avoid extremes of practice while reflecting the heterogeneity of routine care. The use of standardised outcome measures will support future comparison and synthesis with other trials in this area.

Other aspects of the internal validity of the study, the degree to which results represent 'the truth' in the studied population, should also be considered. The authors used a number of suitable strategies to minimise bias within the trial including centralised randomisation and prior publication of the planned analyses. However, some vulnerabilities common to smaller trials of GDHT interventions remain. Whilst it is well recognised that fully masking trial group allocation is not feasible, in this study both attending clinicians and outcome assessors were aware of group allocation, raising the possibility of both intervention and observer bias. The smaller size of this trial, although suitable for an early exploration of a novel approach to GDHT, when combined with a small difference in the primary outcome rate between the groups, leads to a low fragility index. This means that if a very small number of participants had experienced an alternative outcome, the reported results would be reversed. For the robustness of the results this is a particular concern, as a relatively high proportion of participants were excluded from the analysis after randomisation. For example, around 5% of intervention participants and 8% of control group participants were excluded because they had not undergone a long enough operation or not received more than 2 L of fluid, albeit in line with the prespecified plan.

A much larger trial would give more confidence in the treatment effect size seen. However, large conventional RCTs with sample sizes in the thousands bring multiple challenges, are costly, and take years to complete. They are most suitable for testing the real-world clinical effectiveness of final iterations of complex interventions that already have a strong suggestion of benefit from earlier trials. How then do we robustly test novel haemodynamic approaches while avoiding the limitations of smaller trials? Alternative trial designs could address this problem in the future. Recruitment might be accelerated by novel strategies such as point of care randomisation. Outcomes data collection could be facilitated by linkage to existing clinical datasets and by minimising the number of outcome measures.[9] These two features should favour faster recruitment of large sample sizes in otherwise traditional RCTs.

Platform trials with master protocols can be designed to test multiple intervention arms concurrently. This offers the opportunity to test multiple variations of haemodynamic approaches without the time and financial cost of setting up and running multiple separate trials. However, it should be remembered that most of these adaptive trial designs have so far been used on simpler pharmacological interventions.[10] Attempting to test multiple varieties of a complex perioperative intervention could be prone to contamination of the control group, where approaches in one treatment arm spill over into others. Lastly, trials that randomise clusters of participants (e.g. at hospital level) can streamline participant recruitment and reduce control group contamination, albeit at the expense of a larger overall sample size. Such designs have already been used in the evaluation of complex perioperative interventions.[11,12] Although these approaches have limitations, their adoption could mean that a variety of new approaches to GDHT are explored and evaluated more rapidly, economically, and efficiently.

Returning to this iteration of GDHT and whether it merits further investigation, I agree with the authors that this does not appear to be a promising approach. Although the concept of matching treatment targets to individual patients' physiology is sound, the popular prior approach of seeking relative

increases in stroke volume as a marker of fluid responsiveness once anaesthesia is established already individualises fluid dosing to a patient's cardiac performance to volume relationship curve. It is possible that the net fluid loading for the intervention patients in this trial would have been broadly similar if this more conventional approach had been taken. The place of inodilators such as dobutamine within GDHT algorithms remains uncertain. Although experimental and earlier trial work suggest benefit attributable to improvements in microvascular flow and tissue oxygenation,[13] elsewhere concerns have been raised about a potentially deleterious effect on parasympathetic function.[8] The large OPTIMISE II trial,[14] in which fixed low-dose inodilators were used routinely in the GDHT intervention, might help address this uncertainty.

A broader question also remains about the importance of perioperative haemodynamic approaches in altering postoperative outcomes. It is possible that background improvements in surgical and perioperative care and outcomes have diluted the impact of structured GDHT approaches seen in earlier studies, and smaller effect sizes are to be expected.[15] In the wider context, current trial participants might have better cardiovascular health than those 40 years ago. The intervening years have seen a steady increase in cardiovascular medication use and a decline in non-perioperative cardiovascular mortality.[16] It is possible that patients now have less to gain from interventions aiming to improve cardiovascular performance in the perioperative setting. Once again, large trials in both planned and emergency surgery will provide data in the near future on the effectiveness of a well-developed and simplified approach to GDHT.[9,14]

Regardless of these results, there remain strong suggestions that fluid and haemodynamic therapy affect patient outcomes in the contemporary setting.[17,18] We are likely to see further developments in this area. These might relate to technological advances that integrate a wider range of physiological information and provide assistance in addressing the targets of therapy.[19] In parallel, well-founded attempts to tailor our approach to what is likely to be most beneficial for a particular patient, surgery, or combination might focus on identifying those patients most likely to benefit from these more advanced approaches,[8] or on approaches with alternative individualised haemodynamic targets.[20] By embracing novel and efficient evaluation methods we should be able to explore these developments in a matter of years rather than decades.

Declaration of interest

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References

1. Diaper J, Schiffer E, Barcelos GK, et al. Goal-directed hemodynamic therapy versus restrictive normovolemic therapy in major open abdominal surgery: a randomized controlled trial. *Surgery* 2021; **169**: 1164–74
2. de Waal EEC, Frank M, Scheeren TWL, et al. Perioperative goal-directed therapy in high-risk abdominal surgery. A multicenter randomized controlled superiority trial. *J Clin Anesth* 2021; **75**, 110506
3. Aaen AA, Voldby AW, Storm N, et al. Goal-directed fluid therapy in emergency abdominal surgery: a randomised multicentre trial. *Br J Anaesth* 2021; **127**: 521–31
4. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low–moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). *Br J Anaesth* 2018; **120**: 734–44
5. Funcke S, Schmidt G, Bergholz A, et al. Cardiac index-guided therapy to maintain optimised postinduction cardiac index in high-risk patients having major open abdominal surgery: the multicentre randomised iPEGASUS trial. *Br J Anaesth* 2024; **133**: 277–87
6. Grocott MPW, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev* 2012; **11**: CD004082
7. Nicklas JY, Diener O, Leistenschneider M, et al. Personalised haemodynamic management targeting baseline cardiac index in high-risk patients undergoing major abdominal surgery: a randomised single-centre clinical trial. *Br J Anaesth* 2020; **125**: 122–32
8. Ackland GL, Iqbal S, Paredes LG, et al. Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. *Lancet Respir Med* 2015; **3**: 33–41
9. Edwards MR, Forbes G, Walker N, et al. Fluid Optimisation in Emergency Laparotomy (FLO-ELA) Trial: study protocol for a multi-centre randomised trial of cardiac output-guided fluid therapy compared to usual care in patients undergoing major emergency gastrointestinal surgery. *Trials* 2023; **24**: 313
10. Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019; **20**: 572
11. Peden CJ, Stephens T, Martin G, et al. Effectiveness of a national quality improvement programme to improve survival after emergency abdominal surgery (EPOCH): a stepped-wedge cluster-randomised trial. *Lancet* 2019; **393**: P2213–21
12. Fleischman AN, Tarabichi M, Foltz C, et al. Cluster-randomized trial of opiate-sparing analgesia after discharge from elective hip surgery. *J Am Coll Surg* 2019; **229**: 335–345.e5
13. Jhanji S, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM. Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. *Crit Care* 2010; **14**: R151
14. Edwards MR, Forbes G, MacDonald N, et al. Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial: study protocol for a multicentre international trial of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with usual care in patients undergoing major elective gastrointestinal surgery. *BMJ Open* 2019; **9**, e023455
15. Jessen MK, Vallentin MF, Holmberg MJ, et al. Goal-directed haemodynamic therapy during general anaesthesia for noncardiac surgery: a systematic review and meta-analysis. *Br J Anaesth* 2022; **128**: 416–33
16. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart* 2016; **102**: 1945–52

17. Thacker JKM, Mountford WK, Ernst FR, Krukas MR, Mythen MMG. Perioperative fluid utilization variability and association with outcomes: considerations for enhanced recovery efforts in sample US surgical populations. *Ann Surg* 2016; **263**: 502–10
18. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med* 2018; **378**: 2263–74
19. Spataru A, Eiben P, Pluddemann A. Performance of closed-loop systems for intravenous drug administration: a systematic review and meta-analysis of randomised controlled trials. *J Clin Monit Comput* 2024; **38**: 5–18
20. Wijeysundera DN, Duncan D, Moreno Garijo J, et al. A randomised controlled feasibility trial of a clinical protocol to manage hypotension during major non-cardiac surgery. *Anaesthesia* 2022; **77**: 795–807